UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,407	03/25/2005	Victor Willem Van Beusechem	253-9	9615

24336 7590 03/21/2007

KEUSEY, TUTUNJIAN & BITETTO, P.C.
20 CROSSWAYS PARK NORTH
SUITE 210
WOODBURY, NY 11797

EXAMINER	
LONG, SCOTT	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,407	VAN BEUSECHEM ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *10, 15-17 and 19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-14,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-25 are pending. Claim 10 has been withdrawn by the applicant. Claim 18 has been canceled by the applicant. Claims 15-17 and 19-23 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-9, 11-14, and 24-25 are under current examination.

Priority

This application claims benefit from foreign Application No. EP/02075108.7, filed 14 January 2002 and PCT Application No. PCT/EP03/00340, filed 14 January 2003.

The instant application has been granted the benefit date, 14 January 2002, from the application EP/02075108.7.

Specification

Receipt of applicant's amendments to the specification, see page 42, lines 9-23, filed 5 February 2007, is hereby acknowledged by examiner. No new matter was introduced. Examiner withdraws his objection to the specification.

Response to Arguments - Claim Rejections 35 USC § 112

Response to Arguments – 35 USC 112, second paragraph

Applicant's arguments, see page 7-8, filed 5 February 2007, with respect to claim 25 has been fully considered and is persuasive. The examiner thanks the applicant for clarifying the differences between the Fueyo et al. reference and the sequence (SEQ ID NO:5) taught by the instant application. A typo is present in the Fueyo et al. reference, not in the instant application. The rejection of Claim 25, under 35 USC 112, second paragraph, is hereby withdrawn.

Response to Arguments – ENABLEMENT (35 USC 112, first paragraph)

Applicant's arguments filed 5 February 2007 have been fully considered but they are not persuasive.

The applicant has addressed certain aspects of the rejections of Claims 5-6 and 8 under 35 USC 112, first paragraph, as failing to enable for p53 dependent apoptosis based on activity of E1B-55kDa protein, E1B19kDa protein, and E4orf6 protein. The examiner accepts the results of experiments presented in Figure 7 and described on page 20, line 31 to page 21, line 3 of the specification and also in the REMARKS (page 9, paragraphs 2-3). However, the examiner does not accept the applicant's conclusion that the comparison of viruses AdΔ55K-p53 and AdΔ24-p53 demonstrate that the presence or absence of E1b-55kDa protein and consequent cell death (apoptosis) is based merely on the addition of the gene for E1b-55kDa protein.

The applicant refers to the AdΔ24-p53 virus as "E1B-55k positive virus", which indeed it is; however, the AdΔ24-p53 virus is also an E1A negative virus (described in REMARKS, page 9, parag. 2). This is extremely important to note, because the state of the art, Debbas and White, state that "the amino terminus of E1A is required for induction of cellular DNA synthesis, enhancer repression, and transformation" (page 551, col.1). Without functional E1A, p53-mediated apoptosis will be affected. An alternative interpretation of the results in the Figure 7 experiment could be that the absence of E1A function, as in the AdΔ24-p53 virus, is responsible for increased apoptosis, rather than the presence of E1B-55k. Or perhaps, the combination of E1A deletions and the presence of E1B-55k and wild-type p53 are responsible for enhanced apoptosis. Merely the inclusion of E1B proteins (claims 5-6 and 8) in an adenovirus seems to be insufficient for apoptosis. The example and interpretation offered by the applicant cannot overcome the examiner's rejection.

Therefore, the rejection of claims 5-6 and 8 under 35 USC 112, first paragraph is hereby maintained.

Response to Arguments - Claim Rejections 35 USC § 102

Applicant's arguments, see REMARKS, page 10-11, filed 5 February 2007, with respect to claims 1-2, 9, and 24-25 has been fully considered and are not persuasive.

The applicant essentially argues that since the E1A-Δ24 protein cannot bind Rb, that the lytic activity demonstrated by the Fueyo et al. cannot be caused by a restoration

of an Rb/p53 apoptotic pathway. Particularly, the applicant asserts, "if an apoptosis pathway is present in these cells it is functional irrespective of the E1A Δ24 protein." (page 11, parag.2). These are interesting points that the applicant raises.

First, it is very clear from the applicants' arguments, that the only limitation that is being challenged in the Fueyo et al. reference is that the virus "compris[es] in the genome...the coding sequence of at least one restoring factor functional in restoring the p53 apoptosis pathway in said target cells". Fueyo et al. have demonstrated that apoptosis has been induced in "mutant-p53 cells" (page 7, col.1, *Treatment with Δ24*). The question seems to be how apoptosis was induced in cells that are "hampered in the p53 dependent pathway." According to the method for constructing the E1A-Δ24 adenovirus (page 8), the E1A-Δ24 virus seems to possess a fully functional genome comprising every gene represented in a wild-type type 5 adenovirus except for the mutant E1A gene (comprising a deletion of 8 amino acids). While it is not clear which of the other adenoviral genes are involved in restoring the hampered p53-dependent pathway, it is clear that at least one of the adenoviral genes is responsible for the apoptosis caused by the introduction of the mutant virus into "mutant-p53 cells". Therefore, the examiner continues to assert that the Fueyo et al. reference teaches each and every limitation of the rejected claims.

Therefore, the rejection of claims 1-2, 9, and 24-25, under 35 USC 102(b), is hereby maintained.

Applicant's arguments, see REMARKS, page 10-11, filed 5 February 2007, with respect to rejection of claims 1-7, 14, and 24 under 35 USC 102(b) as anticipated by Chang et al. have been fully considered and are persuasive. The examiner hereby withdraws the rejection of claims 1-7, 14, and 24 under 35 USC 102(b).

Response to Arguments - Claim Rejections 35 USC § 103

Applicant's arguments (REMARKS, page 13-15), filed 5 February 2007, with respect to rejection of claims 1 and 11-13 under 35 USC 103 have been fully considered and they are not persuasive.

The examiner withdraws the rejection of claims 1 and 11-13 under 35 USC 103, based on Lin et al in view of Chang et al.

The applicant argues that a skilled artisan would not use the modified p53 of the Lin et al. reference to construct a replication competent recombinant adenovirus. The applicant goes to great lengths to describe the deficiencies of the replication defective adenovirus of Lin et al. Among the arguments included in the applicants remarks is that the activity of the p53/adenoviruses of Lin et al. is "completely different from the activity of the claimed viruses of the present invention." (REMARKS, page 14) and "furthermore, Lin does not teach or suggest the enhanced oncolytic effect of the viruses of the present invention" (REMARKS, page 15).

The examiner reasserts that it is upon the combination of the p53 of Lin et al. and the replication competent recombinant adenoviruses of Chang et al. that an obviousness rejection was made and not simply upon Lin et al alone. As for the asserted "lack of apoptotic activity" of the modified p53 of Lin et al., the examiner also reasserts that Lin et al. teach that the adenovirus restores function in cells "which lack endogenous p53" (Transcriptional Activation, p. 5896) and "induce...apoptosis at similar levels to adenovirus *wt*-p53" (Transcriptional Activation, p.5896). Therefore, the combination of Lin and Chang would also induce apoptosis in cells that are hampered in the p53-dependent pathway. The applicant asserts that Lin does not teach "enhanced oncolytic effect," but "enhancement" is not claimed in the instant invention. Only "restoring the p53 apoptosis pathway in target cells" is claimed in the instant invention. Lin et al., in fact, teaches the same, as cited above.

Therefore, the rejection of claims 1 and 11-13 under 35 USC 103(a), is hereby maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11-14 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901) in view of Chang et al.

Lin at al. teach an adenovirus "p53 variant (p53 14/19) containing double substitutions at amino acid residues Leu-14 and Phe-19... p53 14/19 is deficient in mdm2 binding" (Results, p.5896). Lin et al. also teach that the adenovirus restores function in cells "which lack endogenous p53" (Transcriptional Activation, p. 5896) and "induce...apoptosis at similar levels to adenovirus *wt*-p53" (Transcriptional Activation, p.5896)

Lin et al. does not teach the replication competent adenovirus, but rather a replication defective p53 adenovirus. Lin et al. also do not teach tissue specific conditional replication.

The teachings of Chang et al. are described below. Chang et al.teach many of the limitations of claim 1, including a "cell-specific...recombinant...adenovirus"

(abstract) which is "replication competent" (column 32, line 21), "replication-conditional" (abstract) and can "provide a therapeutic benefit in a tissue...from one or more heterologous gene products expressed from the vector" (abstract). While Chang et al does not explicitly teach that the target cells are hampered in the p53 dependent apoptosis pathway, Lin et al. do teach restoration of p53 dependent apoptosis.

Claims 2 and 24 are directed to "human adenovirus" of "serotype 5". Chang et al teach the limitations of claims 2 and 24, a "human adenovirus 5" (column 4, line 1).

Claim 3 is directed to "early adenovirus gene is controlled by a tumor-specific promoter." Chang et al teach the limitation of claim 3 that "a gene in the adenovirus E1 region is operably linked to the tissue-specific transcriptional regulatory control sequence. Preferably the E1a, E1b, or E2a" (column 7, lines 34-39). Chang et al. further teach the "tumor-specific promoter" (column 7, line 49).

Claim 4 is directed to a "trans-complemented adenovirus." Chang et al. teach the further limitation of claim 4 that "replication is conditioned upon the presence of a trans-acting transcriptional factor " (Col 5, lines 9-10).

Claims 5-6 are directed to the "E1B-55kDa protein" and "E1B-19kDa protein." Chang et al. teach the limitations of claims 5-6 that "the invention further embodies the use of...vectors having...essential regions...for replication...E1b19 kDa gene, or E1b 55 kDa gene" (column 17, lines 20-23).

Claim 7 is directed to "genes of the...E4 region." Chang et al. teach the limitation of claim 7, "E4 coding region" (column 17, line 18).

Claim 8 is directed to "the gene encoding...E4orf6 protein." The limitation of claim 8, E4orf6, is inherent in the E4 coding region, as described by Moore et al., "wild-type E4 genes...express the E4orf6" (p.11301).

Claim 14 is directed to "target cell is a human...cancer cells, arthritic cells, smooth muscle cells, and cells infected with a virus." Chang et al teach the limitation of claim 14 that the target cells are "tumors, ...arthritis" (column 23, lines 50-57), and "tumor types include...soft tissue...reproductive tract" (column 23, lines 47-48). Vascular smooth muscle cells are an inherent sub-type of soft tissue. The tumors of the reproductive tract include cervical cancer which is commonly caused by human papilloma virus. Chang et al. teach activation of their tissue specific adenoviruses through "transcriptional regulatory factors include...transactivating factors produced by endogenous viral sequences such as from CMV, HIV, EBV, HSV, SV40, and other such viruses that are pathogenic...in humans" (column 9, lines 43-47). Therefore target cells infected with viruses other than the therapeutic adenovirus is taught by Chang et al.

Chang et al. teach the further limitation of claim 22 that "the methods of treatment...the tissue is abnormally proliferating, and is especially tumor tissue." (column 7, lines 11-13).

Chang et al. does not teach the limitations of claims 11-13, specifically that the restoring factor is p53 and that the p53 protein lacks a functional MDM2 binding domain and a functional derivative of human p53 mutated with amino acids Leu-14 and Phe-19. These limitations are taught by Lin et al. as described above. While Chang et al does

not explicitly teach that the target cells are hampered in the p53 dependent apoptosis pathway, Lin et al. do teach restoration of p53 dependent apoptosis.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to incorporate the tissue specific replication conditional control features of Chang et al into the adenovirus p53 construct of Lin et al. which contains mutations to the MDM-2 binding site of p53.

The person of ordinary skill in the art would have been motivated to make those modifications because "p53 14/19 modified tumor suppressor gene may be a promising therapeutic agent for human cancers that express abnormally high levels of mdm2 oncogene product" (Lin et al., abstract. P.5895). Lin et al would have been motivated to incorporate the modifications of Chang et al, because the adenovirus of Lin et al. is directed to "mdm2 gene amplification in tumor types...soft tissue sarcomas, " (Introduction, p.5895). The tissue specific adenovirus of Chang et al. is suited to "tumor types include...soft tissue sarcoma" (column 23, line 47). The combined adenovirus could have enhanced anticancer effects through the addition of the improvements to the known tumor suppressor, p53, and the augmented killing effect created as the replicating virus spread its effect throughout the soft tissue sarcomas.

At the time the invention was made, there would have been a reasonable likelihood of success because the state of the art involving mutagenesis and adenoviruses were commonly practiced.

Therefore the method as taught by Lin et al. in view of Chang et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott Long
Patent Examiner
Art Unit 1633

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER